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10/036,988	12/31/2001	Roger L. Papke	UF-293	5315

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EXAMINER
KWON, BRIAN YONG S

ART UNIT	PAPER NUMBER
1614	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/036,988	PAPKE, ROGER L.	
	Examiner	Art Unit	
	Brian S Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *11-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's Response to Restriction Requirement

1. Applicant's election with the Group I, claims 1-10, is acknowledged. Claims 11-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

Information Disclosure Statement

2. Enclosed is an initialed copy of PTO 1449 which has been considered for your records, Application No. 10/036,988.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the combination of metanicotine or a pharmaceutically acceptable salt and the specific compound(s) having antagonistic activity or mixed agonist/antagonist activity toward the specific nicotinic acetylcholine receptor subtypes, for example DMXB on $\alpha 3\beta 4$ receptor for the treatment of the specific neurological condition(s) (e.g., Alzheimer's disease, Parkinson's disease, attention deficit disorder, etc...), does not reasonably provide enablement for using "analogue thereof" and "at least one compound exhibiting antagonistic activity, or both agonist and antagonist activity, toward one or more nicotinic acetylcholine receptor subtypes" for the treatment of a neurological condition characterized by dysfunction of nicotinic

acetylcholine receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention relates to a method of treating neurological condition characterized by dysfunction of nicotinic acetylcholine receptors comprising administering combination of metanicotine, or a pharmaceutically acceptable salt or analogue thereof, and at least one compound exhibiting antagonistic activity, or both agonist and antagonist activity, toward one or more nicotinic acetylcholine receptor subtypes.

(2) The state of the prior art

The art recognizes the use of nicotinic compounds capable of non-selectively interacting with nicotinic cholinergic receptors or selectively interacting with the specific

nicotinic cholinergic receptor subtypes (e.g., α4β2, α4β4, α3β4) for the treatment of certain neurological disorders characterized by dysfunction of nicotinic acetylcholine receptors, fore example Alzheimer, Parkinson's disease, Tourette's syndrome, attention deficit disorder and schizophrenia.

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art.

(5) The breadth of the claims

The claims are very broad due to the vast number of possible neurological conditions characterized by dysfunction of vast number of possible nicotinic acetylcholine receptors, the vast number of possible compounds exhibiting nAChRs antagonistic or mixed agonist/antagonist activity or their analogues or metanicotine analogues thereof toward the vast number of possible nicotinic acetylcholine receptor

subtypes. The complex nature of pharmacology of neuronal nicotinic receptors is also recognized by applicant and well illustrated in the specification (page 2, para. 4 thru page 3, para. 6). The specification states: "With a gene family that includes at least nine different α subunits (designated α2-α10) that in some cases may function as homooligomers (α7-α10) or alternatively combine with different neuronal β subunits (β2-β4), there is a great potential for structural diversity just on the level of the basic pentamer receptor subunit combinations...Furthermore, nicotinic receptor subunits exhibit considerable promiscuity in their ability to coassemble to form functional channels in various expression systems. Therefore, its possible that alternative subunit combinations may result under certain conditions...".

(6) The amount of direction or guidance presented

The specification discloses examples of acetylcholine, nicotine, GTS-21, ABT-089, ABT-418, ABT-594, SIB-1508Y, SIB-1533A, epibatadine as mixed nAChR agonists/antagonists, mecamylamine as nAChR antagonist and metanicotine as a nAChR activator (agonist), more specifically DMXB as mixed nAChR agonists/antagonists having α3β4 activity and metanicotine as α4β2 activator (page 5, para. 13; Table I). However, the specification provides no guidance, in the way of enablement for "analogue thereof" and "at least one compound exhibiting antagonistic activity, or both agonist and antagonist activity, toward one or more nicotinic acetylcholine receptor subtypes" other than disclosed examples. Furthermore, the specification fails to provide sufficient information or guidance that all "neurological condition characterized by dysfunction of nicotinic acetylcholine receptors" can be treated by the numerous possible combinations

of the claimed compounds, other than disclosed examples of neurological conditions (e.g., Alzheimer's disease, Parkinson's disease, Huntington's chorea, etc...). The specification fails to provide information allowing the skilled artisan to ascertain the specificity of the claimed compounds (other than disclosed examples) with respect to nAChRs subtypes without undue amount of experimentation. The specification does not provide sufficient guidance or information regarding how to ascertain which compounds of priori will work on which subtypes of nAChRs. In view of the nature of the invention, the amount of guidance present in the specification, and the breadth of the claims, it would take undue trials and errors to determine the selectivity of the claimed compounds with respect to receptor subtype specificity. Furthermore, undue amount of experimentation is required to treat the entire scope of claimed neurological conditions wherein the manifestation of certain pathological conditions are varied depending on the involvement of various nicotinic receptor subunits combinations.

(7) The presence or absence of working examples

As stated above, the specification discloses examples of acetylcholine, nicotine, GTS-21, ABT-089, ABT-418, ABT-594, SIB-1508Y, SIB-1533A, epibatadine as mixed nAChR agonists/antagonists; mecamylamine as nAChR antagonist. No examples of "analogues" of metanicotine and nAChR antagonist or mixed nAChR agonist/antagonist are provided in the specification.

(8) The quantity of experimentation necessary

Since the significance of particular metanicotine analogues or nAChR antagonist or mixed nAChR agonist/antagonist for different aspects of biological activity with to

receptor subtype specificity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue amount of experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crooks et al. (US 5616707) in view of Newhouse et al. (Society of Biological Psychiatry, (Feb. 2001), 49:268-278).

Crooks teaches or suggests the use of (E)-N-methyl-4-[3-(6-methyppyridin)yl]-3-butene-1-amine (metanicotine), in an amount sufficient to pass across the blood-brain barrier of the subject, for the treatment of Alzheimer's disease wherein without causing significant activation of receptors associated with undesirable side effects (abstract; column 1, lines 24-61; column 4, lines 38-44; column 11, lines 26-36; column 12, lines 46-50).

Newhouse teaches or suggests the use of the claimed mixed nAChRs agonist/antagonist such as ABT-418 ($\alpha 4\beta 2$ selective agent, known as (S)-3-methyl-S-(1-methyl-2pyrrolidinyl)isoxazole) for the treatment of Alzheimer's disease. Newhouse also teaches or suggests the advantage of using such selective agents in the treatment of Alzheimer due to their greater therapeutic index and improved safety profile. See abstract; page 270, column 2, para. 2 thru page 272, column 1, para. 1 ; page 274, column 1, para. 1).

The teaching of Crooks differs from the claimed invention in the combination use of metanicotin and ABT-418 for the treatment of said neurological condition, namely Alzheimer's disease. To incorporate such teaching into the teaching of Crooks, would have been obvious in view of Newhouse who teaches or suggests the use of ABT-418 ($\alpha 4\beta 2$ selective agent), GTS-21 ($\alpha 7$ selective agent) and SIB-1553A ($\alpha 4\beta 2$ selective

agent) for the treatment of Alzheimer's diseases and the advantage of using selective nicotinic agonists in the treatment of Alzheimer due to their greater therapeutic index and improved safety profile.

Above references in combination make clear that metanicotine and mixed nAChRs agonist/antagonist such as ABT-418 have been individually used for the treatment of Alzheimer's disease. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

One having ordinary skill in the art would have been motivated to make such modification such that the combination of metanicotine and ABT-428 would provide enhanced therapeutic effect in treating Alzheimer's disease while providing less adverse effects that may be resulted from activation of receptors associated with undesirable side effects.

Conclusion

5. No Claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (703) 308-5377. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax number for this Group is (703) 308-4556.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brian Kwon

ZOHREH FAY
PRIMARY EXAMINER
GROUP 1600

Zohreh Fay